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CLINICAL ARTICLE

Towards improving the safety and diagnostic yield of stereotactic biopsy in a single centre

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Abstract
Background Previously, we reported on our single centre results regarding the diagnostic yield of stereotactic needle biopsies of brain lesions. The yield then (1996–2006) was 89.4%. In the present study, we review and evaluate our experience with intraoperative frozen-section histopathologic diagnosis on-demand in order to improve the diagnostic yield.
Methods One hundred sixty-four consecutive frameless biopsy procedures in 160 patients (group 1, 2006–2010) were compared with the historic control group (group 2, n=164 frameless biopsy procedures). Diagnostic yield, as well as demographics, morbidity and mortality, was compared. Statistical analysis was performed by Student's t, Mann–Whitney U, Chi-square test and backward logistic regression when appropriate.
Results Demographics were comparable. In group 1, a non-diagnostic tissue specimen was obtained in 1.8%, compared to 11.0% in group 2 (p=0.001). Also, both the operating time and the number of biopsies needed were decreased significantly. Procedure-related mortality decreased from 3.7% to 0.6% (p=0.121). Multivariate analysis only proved operating time (odds ratio (OR), 1.012; 95% confidence interval (CI), 1.000–1.025; p=0.043), a right-sided lesion (OR, 3.183; 95% CI, 1.217–8.322; p=0.018) and on-demand intraoperative histology (OR, 0.175; 95% CI, 0.050–0.618; p=0.007) important factors predicting non-diagnostic biopsies.
Conclusions The importance of a reliable pathological diagnosis as obtained by biopsy must not be underestimated. We believe that when performing stereotactic biopsy for intracranial lesions, next to minimising morbidity, one should strive for as high a positive yield as possible. In the present single centre retrospective series, we have shown that using a standardised procedure and careful on-demand intraoperative frozen-section analysis can improve the diagnostic yield of stereotactic brain biopsy procedures as compared to a historical series.

Keywords Cerebral biopsy · Diagnostic yield · On-demand histopathology

Introduction

In an earlier report, we demonstrated our single centre results with both frame-based and frameless neuronavigational image-guided techniques in the context of needle biopsies of brain lesions [7]. We reported no differences in diagnostic yield, complications and biopsy-related mortality between both techniques, as corroborated by others [36, 40, 41].

On the matter of diagnostic yield, we discussed the possible importance of intraoperative frozen-section or cytological smear preparations. Our previous results, when no intraoperative histological diagnosis was readily available, showed an overall diagnostic yield of 89.4%, which is on the lower spectrum of yield reported by others [1, 9, 11, 12, 17, 19, 34, 36, 40]. We believe that neurosurgeons should strive for as high a diagnostic yield as possible, respecting the possible morbidity or even mortality,

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although small, the patient confronts when undergoing an intracranial biopsy procedure. Since several authors have shown the benefit of intraoperative histopathologic diagnosis and/or the use of modern intraoperative imaging techniques, improving the diagnostic yield up to as high as 99.2% [4, 14, 20, 22, 31, 32], we implemented intraoperative histopathologic diagnosis into our standardised biopsy procedure in order to possibly improve on our results.

In the present study, we reviewed and evaluated our experience with the use of intraoperative frozen-section diagnosis on-demand, when the neurosurgeon performing the biopsy on macroscopic observation was hesitant about the pathologic nature of the tissue sample.

Patients and methods

We reviewed a consecutive series of patients who had undergone an image-guided stereotactic intracranial biopsy procedure at the Erasmus MC from November 2006 until January 2010. This series of patients succeeded the series of 465 uninterrupted cerebral biopsies, of which 164 were frameless biopsy procedures, published in our earlier report [7]. The data were prospectively gathered, but reviewed in a retrospective manner. One hundred sixty-four frameless biopsy procedures were performed in 160 patients.

Patient and pre-operative neuroimaging characteristics

Age, gender, post-operative biopsy-related complications (morbidity) and mortality, duration of hospital stay as well as operating time, biopsy method used, number of biopsies and complications were extracted from case notes and operative reports. The site of the targeted lesion was obtained from pre-operative computed tomographic or magnetic resonance (MR) imaging. The eventual diagnosis was obtained from the pathological report, from which the diagnostic yield was determined.

Operative technique

The techniques of frameless image-guided stereotactic biopsies applied in our centre have been described previously [7]. One hundred sixty-four biopsies were performed using the frameless stereotaxy protocol under general anaesthesia and head-fixation in a three-point Mayfield clamp. Intraoperative image guidance and the surgical plan were obtained using the Stealth Treon™ system (Medtronic Inc., Minneapolis, MN, USA). Tissue samples approximately 8-mm-long and 1-mm-thick were thus obtained.

In general, four biopsies were obtained at the pre-operatively suggested target, as well as two to four more biopsies at a site proximal to the target on the same biopsy trajectory. The macroscopic aspect of the biopsy was assessed, and it was considered pathological when one or more of the following was observed: (1) glazy/oedematous aspect, (2) haemorrhagic component and (3) dark-greyish aspect. A brain tissue sample was regarded normal when clearly white matter was observed. Intraoperative freeze sectioning was performed, only then when the surgeon was uncertain about the pathologic nature of the tissue sample, i.e. the macroscopic appearance of the acquired tissue resembled normal brain. If diagnostic tissue was not obtained, all parameters and measurements were rechecked to ensure accurate localisation, after which, a repeat biopsy sample could then be sent, via the same or a new trajectory, if need be.

Statistical analysis

Statistical analysis was performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The present 164 biopsies, with the abovementioned standardised procedure and intraoperative histopathologic diagnosis on-demand (group 1), were compared to the historic control of 164 frameless biopsies that were reported previously and did not include intraoperative diagnosis (group 2). Continuous data were compared using the Student's t test for parametric data. For non-parametric data, the Mann–Whitney U test was used. These are presented as mean values±standard deviations, unless otherwise specified. Proportions were compared with Chi-square and Fisher's exact test and presented as percentages. p values <0.05 were considered statistically significant. In order to analyse factors relating to the risk of a non-diagnostic biopsy, the variables selected were dichotomised and initially explored univariately as described above. Variables for which there was not a high probability of association ($p>0.10$) were excluded from the final regression model. Backward stepwise logistic regression was used for this purpose, and odds ratios (OR) and 95% confidence intervals (CI) are presented.

Results

In Table 1, patient and peri-operative characteristics of stereotactic biopsies in patients of group 1 and 2 are shown. There were no differences in age and gender distribution. The peri-operative complication rate was also similar. Interestingly, the number of biopsies taken and the overall operating time both decreased significantly ($p<0.001$ and $p<0.001$, respectively) when comparing with the historical group 2.

The location of the lesion intended for biopsy was not significantly different when compared to side and anatomical site. Left- and right-sided lesions were equally divided (group 1 vs. group 2, 39.0% and 36.0% vs. 39.6% and

Table 1 Patient and peri-operative characteristics of groups 1 and 2

	Group 1 (n=164)	Group 2 (n=164)	p value
Male (%)	55.5	56.7	
Age (years±SD)	52.6±18.4	55.0±17.2	
Operating time (min±SD)	108.5±34.2	127.1±32.8	<0.001
Number of biopsies±SD	7.4±3.3	9.0±3.8	<0.001
Complication (%)			
Haemorrhage	3.0	3.0	
Technical failure	2.4	3.7	

Shown are percentages and mean values±standard deviations (SD). Group 1: period November 2006 until April 2009, with intraoperative histopathological diagnosis on-demand; group 2: period August 1996 until October 2006, without the possibility of intraoperative histopathological diagnosis

40.9%, respectively). In patients of group 1, the three most often biopsied tumours were frontal (22.5%), parietal (22.0%) and thalamic (14.0%) lesions.

Post-operative complications occurred in 14 (8.5%) and 19 (11.6%) of operations in groups 1 and 2, respectively. Of these, four symptomatic haemorrhages in each group (2.4%) were diagnosed by post-operative computed tomography. There was no statistically significant difference between groups 1 and 2 in the frequency of occurrence of post-operative complications. In the most recent patients (group 1), there was one death (0.6%) attributable to the surgical procedure, i.e. death occurring within 30 days as a result of symptomatic post-operative haemorrhage or oedema. There were six biopsy-related deaths (3.7%) in group 2, which did not reach statistical significance (p= 0.121, Fisher's exact).

Diagnostic yield

The overall diagnostic yield of group 1 was 98.2%, i.e. a histological diagnosis was established in 161 of 164 biopsy procedures, whereas in three (1.8%), the biopsy was non-diagnostic. In one patient, this resulted in a repeated biopsy procedure that resulted in the diagnosis of a lymphoma. The second and third patient underwent a subsequent craniotomy when a glioblastoma and metastasis of lung carcinoma was diagnosed, respectively. In 15 cases (8.9%), the surgeon judged the tissue obtained to resemble normal brain and therefore requested for an intraoperative frozen-section diagnosis by the neuropathologist. When non-diagnostic, this prompted for another tissue sample in the chosen trajectory. In the period from August 1996 until October 2006, i.e. group 2, when there was no availability of intraoperative histopathologic diagnosis, the diagnostic yield was only 89.0%, which is statistically lower compared with group 1 diagnostic yield (p=0.001). Table 2 shows the histological diagnoses that were made on the tissue samples taken in both groups. On average, 7.4 (range, 1–19) and 9.0 (1–24) tissue samples were taken during the biopsy procedure in groups 1 and 2, respectively (p<0.001, Table 1).

Table 3 shows the results of the univariate analysis performed to establish the factors related to obtaining a non-diagnostic biopsy specimen (n=21). In the subsequent multivariate regression analysis, only operating time (OR, 1.012; 95% CI, 1.000–1.025; p=0.043), a right-sided lesion (OR, 3.183; 95% CI, 1.217–8.322; p=0.018) and the use of on-demand intraoperative histopathologic examination (OR, 0.175; 95% CI, 0.050–0.618; p=0.007) showed to be important factors.

Discussion

Previously, we have shown the diagnostic yield of stereotactic biopsy either by frame-based or frameless techniques to be equal, as were the morbidity and mortality related to the procedure [7]. The overall diagnostic yield in the previous report was 89.4%, which might be regarded lying on the lower spectrum of the yield obtained by others [1, 9, 11, 12, 17, 19, 34, 36, 40]. The present study suggests that by using on-demand frozen-section analysis of tissue specimens begotten by biopsy, the diagnostic yield can be dramatically improved (98.2%).

Several other authors have corroborated these results, i.e. performing intraoperative frozen-section or cytological smear preparations will increase the rate on a reliable histopathological diagnosis up to as high as 99.2% [4, 14, 17, 29, 31, 38]. McDermott and Bernstein, in *Neuro-oncology: The Essentials* (p. 115), actually state '[…] The management of the failed biopsy begins in the operating room where intraoperative examination of tissue is mandatory to ensure that diagnostic tissue is in fact obtained […]'. Nevertheless, the five most recent reports, illustrating diagnostic yields of 99.3% [35], 94% [30], 90.6% [5], 89.8% [1] and 83.6% [37], do not mention intraoperative pathologic confirmation. Also, in our series, we were not able to perform intraoperative cytological studies in all biopsy procedures. This was primarily due to logistic considerations, such as pressure on the operating theatre regarding time and the unavailability of adequate neuropathologic support on all biopsies. Therefore, we turned to on-demand frozen-section analysis, i.e. the surgeon performing the biopsy assessed the tissue specimen macroscopically as normal brain or pathological tissue sample and, when uncertain, requested the neuropathologist for intraoperative confirmation. Apparently, concluded from the results shown in the present study, there is no need for

Table 2 Histological diagnoses made on tissue samples acquired by stereotactic biopsy

Diagnosis (%)	Group 1 (n=164)	Group 2 (n=164)	p value
Non-diagnostic	1.8	11.0	0.001
Malignant glioma	53.0	51.3	
Low-grade glioma	12.2	14.6	
Lymphoma	14.0	7.9	
Metastasis	3.0	7.3	
Infection/vasculitis/ MS/abscess	12.2	6.7	
Craniopharyngioma cysts	1.8	1.2	
Others[a]	1.8	0	

Shown are percentages. Group 1: period November 2006 until April 2009, with intraoperative histopathological diagnosis on-demand; group 2: period August 1996 until October 2006, without the possibility of intraoperative histopathological diagnosis. Malignant glioma includes astrocytoma, oligoastrocytoma, oligodendroglioma WHO grade III and glioblastoma (WHO grade IV). Low-grade glioma includes astrocytoma, oligoastrocytoma and oligodendroglioma WHO grade II

MS multiple sclerosis

[a] Include meningioma, medulloblastoma, teratoma, malignant peripheral nerve sheath tumour and old haematoma

an intraoperative cytological preparation, and therefore, a neuropathologist standby for every stereotactic cerebral biopsy procedure when an experienced surgeon evaluates the tissue samples obtained. These results are corroborated by the recent article of Shooman et al. who on top of this state that routine intraoperative neuropathological examination is not needed at all [35].

Table 4 shows the diagnostic yield, complication rates, deaths and methods used to ensure a greater diagnostic yield in the most recent biopsy series. Since 2001, a total of 12,038 biopsy procedures are collected in the literature, with an overall diagnostic yield ranging from 83.6% to 100%. Positron emission tomography imaging, MR perfusion and MR imaging spectroscopy integrated into the planning for stereotactic biopsy procedures to determine the trajectory and selection of the appropriate target promise to be important adjuncts to improve diagnostic yield and to decrease sampling error, especially when low-grade gliomas are involved [6, 13, 15, 24, 27, 28, 32, 33]. Recent studies show a yield of 100%, although patient numbers are relatively small [6, 13, 15, 24, 32, 33]. Additional use of metabolic imaging data acquired with MR spectroscopy, more specifically, the ratio of *N*-acetyl aspartate and choline-containing compounds, for target selection can potentially increase the diagnostic efficacy of biopsy procedures.

Another issue to be addressed is the diagnostic accuracy, i.e. the rate of sampling error as established by subsequent open craniotomy. In literature, accuracy rates ranging from 73% to 97% have been reported [2, 7, 17, 30, 40]. Chernov et al. compared the diagnostic efficacy of stereotactic brain biopsy performed with and without additional use of spectroscopic imaging and found that spectroscopy was superior, although not significantly due to the small number of patients, in reaching a diagnosis at all (100% vs. 90%) [6]. Diagnostic accuracy, however, could not be improved by using spectroscopy imaging (67% vs. 79%, MR imaging with and without spectroscopy, respectively).

In the present study, an important difference with the historical control was the use of on-demand intraoperative histological confirmation of pathological tissue, which was

Table 3 Results of univariate analysis to establish confounding factors related to obtaining a non-diagnostic biopsy specimen

	Diagnostic (n=305)	Non-diagnostic (n=21)	p value
Male (%)	55.7	66.6	0.371
Age (years±SD)	53.9±17.7	5.8±18.2	0.828
Tumour side			
Right	38.7	66.7	0.019
Left	38.7	19.0	0.101
Tumour location (frontal, parietal, temporal, etc.)			0.388
Surgeon			0.421
Operating time (min±SD)	116.0±33.4	138.1±39.6	0.004
Number of biopsies±SD	8.3±3.7	7.3±2.7	0.259
On-demand intraoperative frozen-section histology	52.8	14.3	0.001
Peri-operative complication	6.3	4.8	1.000
Post-operative complication	10.5	4.8	0.708
Biopsy-related death	2.3	0	1.000

Shown are percentages and mean values±standard deviations (SD)

confirmed by multivariate analysis to be an important factor to decrease the chance on a non-diagnostic tissue specimen. However, due to the retrospective nature of the present study, some confounding factors should be put forward that may influence the overall results. As a result of technological advance and ease of use, the frameless stereotactic technique has been used more frequently in recent times at our neurosurgical clinic (97.6% vs. 35.3%, respectively). Although we, in concordance with others, have previously shown that this does not influence diagnostic yield [7, 36, 40, 41], Dorward et al. found disagreeing results, concluding that frameless techniques are superior to the gold standard of frame-based biopsy [8]. To exclude this possible confounding factor, we compared the most recent frameless biopsy series (group 1) with the historical control of frameless biopsies only. Furthermore, the effect of an initial learning curve cannot be ruled out. Another, more important factor might be the number of surgeons performing the biopsy procedures. These differ significantly between the historical and the present group of patients. In group 2, a total of 20 surgeons, whereas in group 1, only 15 surgeons were involved with the stereotactic biopsy procedures. In the most recent group (group 1), two surgeons (RD and JWS) performed 51.8% of surgeries and supervised another 12.8%. One might argue that due to a surgeon's increased experience, he/she is apt to

Table 4 Diagnostic yield in recent biopsy series

Author (year)	*n*	Yield	Method to improve yield	Morbidity	Mortality
Kaakaji et al. (2001) [16]	269	97.1	None	3.0	0.4
Paleologos et al. (2001) [31]	125	97.6	Intraoperative histology	2.4	0.8
Ulm et al. (2001) [39]	200	98.5	None	2.0	0
Bhardwaj et al. (2002) [3]	76	98.7	None	2.6	0
Dorward et al. (2002) [8]	155	96.8	Intraoperative histology	16.1	3.2
Gralla et al. (2003) [10]	57	98	Intraoperative histology	3.5	0
Kim et al. (2003) [17]	308	91.7	Intraoperative histology	3.9	0.6
Maia et al. (2004) [24]	21	100	MR perfusion	NA	NA
Pirotte et al. (2004) [32]	32	100	Spectroscopy	NA	NA
Aker et al. (2005) [2]	130	94	Intraoperative histology	0.8	0
Grossman et al. (2005) [11]	355	93.8	None	3.6	0.6
Hemm et al. (2005) [13]	10	100	Spectroscopy	NA	NA
Heper et al. (2005) [14]	130	99.2	Intraoperative histology	0.7	0
McGirt et al. (2005) [26]	270	93	None	5.0	1.0
Smith et al. (2005) [36]	213	90	None	4.0	0.4
Tilgner et al. (2005) [38]	5,000	90.3	Intraoperative histology	2.7	0.7
Ferreira et al. (2006) [9]	170	92	None	2.9	1.2
Shastri-Hurst et al. (2006) [34]	207	89.3	Intraoperative histology	6.4	1.9
Woodworth et al. (2006) [41]	270	90	None	4.0	1.0
Pirotte et al. (2007) [33]	20	100	Spectroscopy	10.0	0
Dammers et al. (2008) [7]	465	89.5	None	11.7	3.9
Hermann et al. (2008) [15]	9	100	Spectroscopy	NA	NA
Kongkham et al. (2008) [18]	622	98.4	Intraoperative histology	6.9	1.3
Lunsford et al. (2008) [23]	1,664	NA	None	3.1	0.1
Landriel et al. (2008) [21]	192	90.6	Intraoperative histology	3.6	2.1
Air et al. (2009) [1]	284	89.8	None	6.7	2.0
Chernov et al. (2009) [6]	69	94	Spectroscopy (100%)	1.4	0
Owen and Linskey (2009) [30]	106	94	None	3.8	0
Teixeira et al. (2009) [37]	176	83.6	None	6.4	0.6
Chen et al. (2009) [5]	299	90.6	None	7.4	1.3
Shooman et al. (2010) [35]	134	99.3	None	2.2	1.5
Total	12,038	94.7 (83.6–100)		4.7 (0.7–16.1)	0.9 (0–3.9)
Present series	164	98.2	On-demand intraoperative histology	8.5	0.6

Diagnostic yield, morbidity and mortality are expressed in percentages

prepare a biopsy trajectory and target that ensures less chance on complications and a higher chance on a positive histological diagnosis. For this, there is no evidence in recent literature as far as we are aware, although Shastri-Hurst et al. touched upon the subject in the "Results" section and found no evidence that the individual performing the biopsy most frequently had better results in terms of complication rate or non-diagnostic rate [34]. Lastly, the recent 164 cases were all histologically examined by one experienced dedicated neuropathologist (JMK), whereas in the past, three pathologists performed the histopathologic diagnosis. A single dedicated neuropathologist might be able to provide a diagnosis more often. Furthermore, the changing tumour classification and grading by the World Health Organisation might aid to construct a more proficient diagnosis nowadays.

The possible advantages of on-demand intraoperative frozen-section analysis are its cost-effectiveness concerning the consultation of a neuropathologist and the need for repeat surgery. More importantly, a non-diagnostic biopsy has an imminent effect on a patient's further treatment. On-demand histopathology, however, demands experienced and dedicated neuro-oncologic trained neurosurgeons [35]. Nevertheless, the issue of diagnostic accuracy, i.e. biopsy sampling error, remains unresolved. As described above, newly available diagnostic techniques might add to locate the adequate biopsy site and decrease sampling error.

Although tumour verification might be warranted, the treating physician should always also consider the morbidity and mortality related to the biopsy procedure. Of the 12,038 procedures in recent literature (Table 4), the average procedure-related morbidity was 4.7% (range, 0.7–16.1%), compared to our own recent series (8.5%). These vary from minor complications to devastating neurological sequelae that can influence a patients' independence. The average mortality rate was 0.9% (range, 0–3.9%) and 0.6% in recent literature and the present series, respectively, from which one might conclude that a brain biopsy is a safe procedure.

Concluding, the importance of a reliable pathological diagnosis as obtained by biopsy, notwithstanding the possibility of sampling error [25, 28], must not be underestimated. Both with regard to the possible risks for the patients, such as (increase of) neurological deficits by oedema or haemorrhage and even death, as well as with regard to the further treatment that might be warranted for each individual patient. In the present single centre retrospective series, we have shown that using a standardised procedure and careful on-demand intraoperative frozen-section analysis, when the macroscopic aspects is not clearly pathological, can improve the diagnostic yield of stereotactic brain biopsy procedures as compared to a historical series.

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Comment

The colleagues of Rotterdam compared the diagnostic yield of frameless stereotactic biopsies with or without the possibility of frozen section and smear preparation assessment during biopsy. The option of asking a neuropathologist to the OR clearly decreased non-diagnostic samples in the final neuropathological evaluation: 1.8% (3 of 164 frameless biopsies 2006-2010) vs. 11% (18 of 160 frameless biopsies 1996-2006). The average numbers of samples were 7.4 vs. 9.0 per patient. Neurosurgeons assessed the macroscopic appearance of the samples as pathologic (oedematous, hemorrhagic, or dark-grayish) - or as normal brain, the only indication for the intra-operative freezesectioning.

The risk of 11% of repeat biopsy and delayed therapy would require reduction – but how?

1. Instant and routine microscopic verification of the presence of representative samples with a putative first diagnosis in the OR – in real life? Neurosurgical units are served by a few neuropathologists at best – often by one or two. Are they willing to walk from their microscopy desks with piles of slide trays to the OR in the other end of the building or in the next one? Few units really have a neuropathologist sitting in the OR until the verification is done.

2. On-demand microscopic assessment in the OR of dubious samples only – as cleverly arranged above.

3. Transfer of fresh samples to the neuropathology unit – and waiting for tens of minutes a phone call from a neuropathologist.

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